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β_2-Microglobulin–derived amyloidosis: An update

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β_2-Microglobulin–derived amyloidosis: An update. The present review attempts to summarize recent developments in the field of β_2-microglobulin–derived amyloidosis ($A\beta_2m$ amyloidosis) in patients on chronic dialysis therapy. A key factor in the pathogenesis is the uremic retention of the precursor molecule, β_2-microglobulin (β_2m). However, secondary modifications of the molecule such as limited proteolysis, conformational changes, and the formation of advanced glycation end products have also been described. Finally, in order to explain the striking predilection of the disease for synovial and periarticular structures, a role of local predisposing factors within the synovial membrane (for example, of the particular constituents of the extracellular matrix) must also be postulated. With respect to clinical symptomatology, recent data have confirmed that clinically manifest signs of the amyloidosis represent only the tip of the iceberg, since histologically amyloid deposition is much more widespread. Noninvasive diagnosing of the disease has been advanced by technical changes of the β_2m scintigraphy. Finally, there is accumulating evidence that prevention of the disease not only includes the usage of high-flux synthetic membranes for hemodialysis or hemodiafiltration, but that other factors contribute to the clinical manifestations of amyloidosis such as the dialysate composition and its microbacteriological quality. Such factors, which have changed over the last years as part of general improvements in dialysis care, may explain why the prevalence of the amyloidosis appears to decrease.

In 1985, Gejyo et al established that a novel type of amyloidosis was present in hemodialysis patients [1]. Initially believed to occur only in chronic hemodialysis patients and hence termed "dialysis associated amyloidosis," it soon became clear that the amyloidosis can develop in patients on any type of renal replacement therapy (with the exception of patients with functioning renal transplants; discussed later in this article) and even in uremic, predialysis patients [2–4]. Therefore, it appears more appropriate to refer to it as "β_2-microglobulin–derived amyloid" or, in consideration of the general amyloid terminology, as "$A\beta_2m$-amyloid" or "AB-amyloid." Although it is a systemic type of amyloidosis, its clinical manifestations are largely confined to the musculoskeletal system.

Key words: hemodialysis, scintigraphy, advanced glycation end product, uremia, proteolysis, synovial membrane.

PATHOGENESIS

Constituents of $A\beta_2m$-amyloid fibrils

β_2-Microglobulin. β_2-Microglobulin (β_2m) is an-11.8 kD protein that is necessary for the expression of HLA class I on the surface of nearly all nucleated cells. Its synthesis rate normally ranges from 2 to 4 mg/kg/day with a half-life of 2.5 hours. Plasma concentrations vary between 1 and 3 mg/mL. Given that 95% of the β_2m elimination is achieved via glomerular filtration, it is not surprising that levels in end-stage renal failure (ESRF) can be elevated up to 60-fold in anuric individuals [2, 3].

While there is no doubt that the increased body burden of β_2m in end-stage renal disease (ESRD) is mainly related to the decreased renal excretory rate, it is less clear whether the β_2m synthesis rate is also altered in uremia. Synthesis and release of β_2m can be stimulated in vitro by exposure of cells to acidosis, endotoxin, or inflammatory cytokines, many of which are present or induced during uremia or dialysis therapy [5, 6]. In vivo evidence for an altered synthesis of β_2m in dialysis patients, however, is limited. The daily synthesis rate of β_2m in patients with uremia has been found to be in the normal range in the majority of dialysis patients [2]. Thus, compared with the massive renal retention of β_2m, changes of its synthetic rate are likely to be of minor importance in vivo.

Amyloid P component. The amyloid P component, derived from serum amyloid P component (SAP), is a ubiquitous constituent of almost all types of amyloid where it binds to the fibrils. It has been proposed that amyloid P component renders the amyloid fibrils resistant to proteolytic degradation in vivo [7].

Proteoglycans. Proteoglycans have been detected in or around $A\beta_2m$-amyloid fibrils [8–10]. Experimental evidence suggests that matrix compounds such as highly sulfated glycosaminoglycans, in particular heparan sulfate proteoglycans, are related to the onset of amyloidosis.

Others. Various antiproteases have been identified in $A\beta_2m$-amyloid deposits [11, 12]. In all instances, however, surrounding tissues also contained these antiproteases, and consequently, it is unclear whether they play a specific role in the persistence of amyloid fibrils. Finally, Brancaccio et al have described immunoglobulin light

chains to represent an intrinsic component of β_2m–derived amyloid fibrils [13].

Pathogenetic concepts

In view of the restriction of Aβ_2m-amyloidosis to uremic patients, the increased body burden of β_2m in uremia appears to be the basic precondition for amyloidogenesis. However, a pure "precipitation theory" is unlikely, since (*1*) β_2m serum levels do not differ between patients with and without the disease, and (*2*) local β_2m concentrations, for example, within synovial fluid, are not increased above the serum concentration [14]. These observations have led to the search for biochemical modifications of the β_2m molecule, which might facilitate its deposition within amyloid fibrils. Some candidates for these modifications include:

Limited proteolysis of native β_2m, similar to mechanisms involved in the pathogenesis of other types of amyloid [15]. However, not all investigators have been able to confirm the presence of cleaved β_2m molecules within Aβ_2m-amyloid [16, 17].

Three-dimensional modifications of the β_2m molecule. Rampino et al developed a monoclonal antibody to a β_2m epitope (amino acids 92 to 99) exposed in Aβ_2m-amyloid but not on cell surface β_2m. They noted that the epitope 92 to 99 is exposed on mononuclear cells following "stress" (heat shock, low pH, etc.) as well as during hemodialysis. Thus, dialysis may induce conformational molecular changes that might contribute to the formation of amyloid (abstract; Rampino et al, *Nephrol Dial Transplant* 14:A229, 1999).

Advanced glycation end products (AGE). Different sugar-protein cross-links have been detected within Aβ_2m-amyloid fibrils, including pentosidine, N^{ϵ}-(carboxymethyl)-lysine, and imidazolone [4, 18–22]. They are presumably the result of oxidative or "carbonyl stress" in chronic dialysis patients [4, 23]. In vitro, AGE-modified β_2m activates monocytes via the AGE-receptor (RAGE) [24]. It may thereby contribute to inflammatory changes surrounding the amyloid [4]. Whether AGE modifications also render β_2m more amyloidogenic or enhance the persistence of established fibrils in tissue is speculative. Furthermore, AGE modifications are not limited to β_2m but occur ubiquitously in dialyzed patients. Another unexplained finding with respect to the role of AGE-formation is the observation that radiological signs of Aβ_2m-amyloid occur with similar frequency in both diabetic and nondiabetic dialysis patients despite the fact that the former have markedly higher circulating AGE levels [25].

None of the aforementioned alterations can explain the distribution pattern of Aβ_2m-amyloidosis. Consequently, local factors, particularly components of the extracellular matrix (for example, proteoglycans; discussed previously in this article), are likely also involved in the amyloidogenesis. In fact, synovial tissue appears to be a predilection site for various amyloidoses, since we noted a considerable number of different amyloid types in synovial tissues from both uremic patients and patients with normal renal function (Table 1) [26]. Local inflammatory changes appear to largely represent the consequence of Aβ_2m-amyloid deposition rather than its origin [26–28]. It has been suggested that interleukin-8, which is overexpressed in joints affected by Aβ_2m-amyloid deposits, may contribute to the recruitment of leukocytes [29], whereas overexpression of transforming growth factor-β (TGF-β) may act as a local profibrogenic factor [30].

Table 1. Synovial amyloid deposition in chronic hemodialysis patients and patients with normal renal function

Type of amyloid	Dialysis patients (N = 36)	Controls (N = 8)
Aβ_2m	19	—
Mixed Aβ_2m and AA	1	—
Transthyretin (senile amyloid)	1	1
Mixed transthyretin and AA	1	—
AA	1	—
κ/λ light chain	—	—
Unknown	3	2

Abbreviations are: Aβ_2m, β_2-derived amyloidosis; AA, amino acids. Immunohistological survey of amyloid types deposited in surgery or autopsy specimens obtained from joint capsules (modified from [26]).

EPIDEMIOLOGY

Histologically, Aβ_2m deposits, in rare instances, may be detected only a few months after the initiation of hemodialysis or even in predialysis patients [2–4, 31]. Aβ_2m-amyloid deposition can precede clinical manifestations by several years. Most amyloid deposits in fact never appear to cause clinically relevant problems. The largest postmortem study available to date noted a considerable discrepancy between clinical and radiological amyloid signs (that is, carpal tunnel syndrome and bone radiolucencies), which were present in 2 and 4%, respectively, of the patients versus the histologic demonstration of Aβ_2m-amyloid in joint samples of 48% of the patients [31]. In that study, prevalences of the amyloid increased to 100% in patients treated for more than 13 years [31]. Both this and our own study confirmed that the joint distribution of Aβ_2m-amyloid is uneven with the sternoclavicular joint and hips showing the highest percentage of positive samples [26, 31]. Clinically and radiologically, Aβ_2m-amyloid–related symptoms are rarely present before five years of therapy. After this time, there is an almost linear increase of the prevalence, which in past evaluations reached nearly 100% after 15 years of treatment (Fig. 1) [2–4].

Aβ_2m-amyloidosis cases have been described with virtually every nontransplant renal replacement therapy [2–4]. Two risk factors for Aβ_2m-amyloid deposition have been

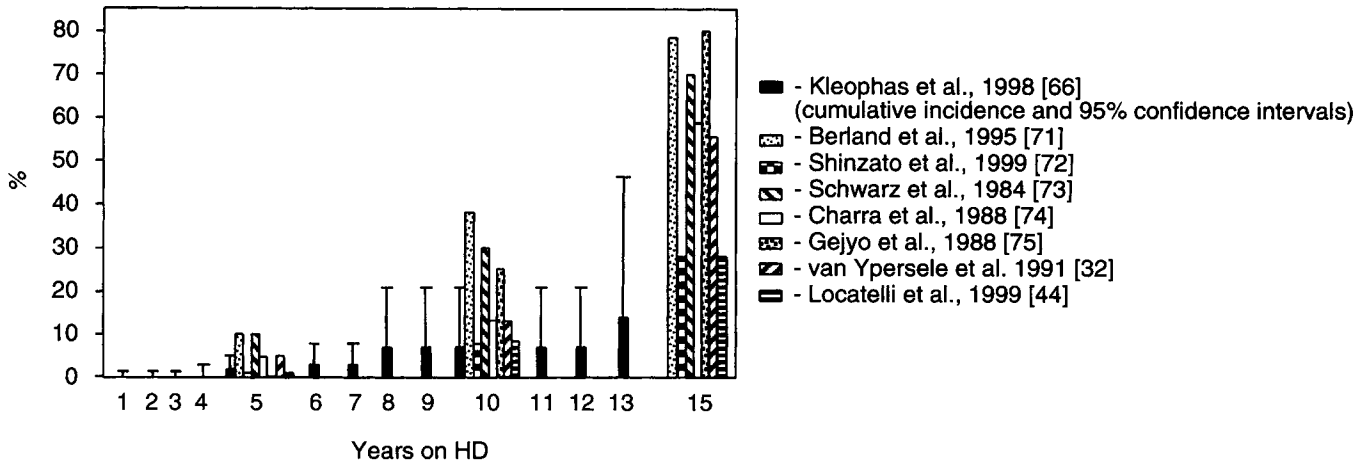

Fig. 1. Summary of studies on the prevalence of carpal tunnel syndrome in patients on chronic hemodialysis using either conventional hemodialysis systems [32, 44, 66, 71–75] or the Genius®-tank dialysis system [66].

identified: age at onset of renal replacement therapy and the duration of (nontransplant) renal replacement therapy [31–33]. In line with these observations, no cases of Aβ_2m-amyloidosis have yet been described in the pediatric dialysis population.

DIAGNOSIS AND CLINICAL MANIFESTATIONS

Clinical manifestations of Aβ_2m-amyloid deposition are largely confined to osteoarticular sites, particularly synovial membranes [2–4, 34]. Clinically relevant organ involvement during Aβ_2m-amyloidosis is rare and largely confined to very long-term patients (that is, >15 years of dialysis). Most reports on organ deposits of Aβ_2m-amyloid only show asymptomatic microscopic foci. As in other types of amyloidosis, some suggestive but no pathognomonic clinical or radiological findings exist in Aβ_2m-amyloidosis. To date, the definitive diagnosis of Aβ_2m-amyloidosis still relies on histologic findings: Congo red staining, immunohistochemical demonstration of the precursor molecule within deposits, and the electron microscopical demonstration of typical fibrils. Fat aspiration or rectal biopsy fail in Aβ_2m-amyloidosis, and diagnostic material usually has to be obtained from synovial membranes or bone lesions [2]. Detritus in the synovial fluid may be used to diagnose Aβ_2m-amyloidosis.

Ultrasonograpy may be used to follow synovial Aβ_2m-amyloid deposits noninvasively. Thickening of the joint capsules, biceps tendons, and the rotator cuffs, as well as echogenic structures between the muscle groups and joint effusions has been observed in long-term hemodialysis patients [35, 36]. Problems of ultrasound relate to the fact that only selected joints are accessible by the examination and that the data are relatively dependent on observer skill.

Radiologically, the affected joints may present with single or multiple juxta-articular cystic bone radiolucencies, preferentially at the insertion sites of capsules and tendons. These cystic bone radiolucencies arise from amyloid deposition in bone and are prone to pathological fractures. However, single small bone cysts may already be observed in 30% of nonuremic patients. Another important differential diagnosis in uremics is brown tumors of secondary hyperparathyroidism. In an attempt to improve the specificity of radiological data, van Ypersele de Strihou et al outlined criteria that provide a high diagnostic likelihood, albeit with low sensitivity, of Aβ_2m-amyloid–induced cystic bone radiolucencies [32]: (*1*) diameter of lesions >5 mm in wrists and >10 mm in shoulders and hips, (*2*) normal joint space adjacent to the bone defect, (*3*) exclusion of small subchondral cysts located in the immediate weight-bearing area of the joint, (*4*) exclusion of defects of the "synovial inclusion" type, (*5*) increase of defect diameter of >30% per year, and (*6*) the presence of defects in at least two joints.

Computed tomography (CT) and magnetic resonance imaging (MRI) may also be used to search for evidence of Aβ_2m-amyloidosis [2, 3, 37], but again, are not specific.

Since amyloid deposits, independent of the specific type, have a relatively high calcium content, conventional ^{99m}Tc-diphosphonate bone scans have been used for their visualization. Three groups have employed such scans in end-stage renal disease patients and described imaging of Aβ_2m deposits by this method [38–40]. However, in two of these latter articles [38, 39], visualization of amyloid deposits was incomplete, as judged by the comparison with clinical and radiological findings. Furthermore, the scan could not distinguish between periarticular amyloid deposition and arthropathies of different origin. A third, more recent study attempted to improve the value of bone scintigraphy by combining it with gallium-67 and thallium-201 scans, which label inflammatory changes

[40]. A notable finding in that study was that abnormal (peri-)articular ^{99m}Tc-MDP accumulations were only detected in 8 of 23 chronic hemodialysis patients who had been on dialysis for 10 to 19 (mean 13) years [40]. This relatively low prevalence of abnormal findings in a long-term dialysis population again raises doubts about the sensitivity of conventional bone scintigraphy for the detection of Aβ_2m-amyloidosis. The addition of gallium-67 and thallium-201 whole body and single photon emission tomography (SPET) images, apart from the additional radiation exposure, further decreased the rate of abnormal findings to 6 out of 23 patients [40]. Thus, clinical applicability of bone scans in cases of Aβ_2m amyloidosis may largely be restricted to following established cases of the disease.

Two scintigraphic methods, employing either radiolabeled SAP or β_2m, have been introduced to render the detection of amyloid deposits more specific. Using ^{123}I-labeled SAP, Aβ_2m deposits have been visualized in several long-term hemodialysis and peritoneal dialysis patients [41, 42]. However, this scan did not show tracer accumulation in other frequently involved sites, such as hips or shoulders, and vice versa frequently labeled the spleen, which is usually spared from Aβ_2m deposits. In contrast, scanning with ^{131}I-labeled β_2m yielded tracer accumulations corresponding to the typical distribution pattern of Aβ_2m [33]. Specificity of this method was shown by several methods, and the sensitivity was found to exceed markedly that of combined clinical and radiological investigations [33, 43]. Recently, both the radiation exposure and the optical resolution of this latter scan have been further refined by substituting ^{131}I with ^{111}In. In a final step, we generated recombinant human β_2m (rhβ_2m). ^{111}In-rhβ_2m again failed to show significant tracer accumulation over joint regions in patients on short-term hemodialysis without evidence of Aβ_2m-amyloidosis. In contrast, local tracer accumulations similar to those observed with natural ^{111}In-labeled β_2m could be demonstrated in long-term HD patients with evidence of Aβ_2m-amyloidosis. Thus, scintigraphy for Aβ_2m-amyloidosis with ^{111}In-labeled rhβ_2m provides a homogenous and safe recombinant protein source and allows for the sensitive and specific noninvasive detection of Aβ_2m-amyloid deposits in dialysis patients.

Carpal tunnel syndrome

Carpal tunnel syndrome is a characteristic, although not pathognomonic, clinical sign of Aβ_2m-amyloidosis [2, 3]. The pain typically exacerbates at night and during hemodialysis. Aβ_2m-amyloid–induced carpal tunnel syndrome usually requires surgical release. In some cases, particularly those manifesting within the first five years of dialysis, other reasons for the carpal tunnel syndrome should be considered, especially the association of carpal tunnel syndrome with diabetes or multiple myeloma. Furthermore, Locatelli et al have noted a more than 5.4-fold increased risk for carpal tunnel in the presence of heart disease in uremic patients [44].

Osteoarthropathy of peripheral joints

This other frequent manifestation of Aβ_2m-amyloidosis is due to local amyloid deposition in articular cartilage, the synovial membrane and villi, tendons as well as in subchondral bone. It is characterized by recurrent or persistent arthralgias, stiffness of large and medium size joints, and swelling of capsules and adjacent tendons [2, 3]. Further symptoms include recurrent joint effusions and synovitis, which most often occur in large joints. In the differential diagnosis, a variety of other conditions, for example, nonamyloid induced bursitis, arthritis or tendinitis or radiculopathy has to be considered.

Other musculoskeletal symptoms caused by Aβ_2m amyloidosis

In present populations of dialysis patients, Aβ_2m-amyloid likely plays a predominant role in the pathogenesis of spondylarthropathy. Aβ_2m deposits have been demonstrated in intervertebral discs, apophysial joints, and ligaments. Clinical symptomatology related to vertebral column involvement in the course of Aβ_2m-amyloidosis may range from asymptomatic deposits to radiculopathy, stiffness, "mechanical" ache, and finally medullary compression with resulting paraplegia or cauda equina syndrome [2, 3].

Apart from carpal tunnel syndrome, various other manifestations of Aβ_2m-amyloidosis can affect the hand of long-term dialysis patients resulting in severe functional deficiencies. Aβ_2m-amyloidosis can also manifest in dialysis patients as subcutaneous tumorous deposits, while diffuse infiltration of the subcutaneous fat or skin has not been observed.

TREATMENT AND PREVENTION

Therapy

Therapy of an established Aβ_2m-amyloidosis can at best be symptomatic, such as the usage of nonsteroidal antiinflammatory drugs, topical steroid ointments plus phonopheresis, and surgical measures, such as carpal tunnel decompression or bone stabilization in areas of "cystic" destruction. Renal transplantation usually leads to symptomatic improvement within days, likely related to the usage of steroids and immunosuppressive drugs [45]. Based on these observations, it has been tested whether steroids (0.1 mg/kg) can be beneficial for Aβ_2m-amyloid-associated severe polyarticular arthropathy in dialysis patients. Preliminary data indeed suggest a high efficacy of the steroids in relieving symptoms [46]. A change of the hemodialysis mode, from treatment with Cuprophane® membranes to so-called biocompatible hemodialyzer mem-

branes, has been claimed to induce symptomatic relief [47], but placebo effects had not been ruled out.

Prevention

Prevention of the development or at least of the clinical manifestations of an Aβ_2m-amyloidosis encompasses different approaches:

Renal transplantation. This is clearly the preventive measure of choice, since the amyloidosis does not occur in the presence of significant renal function and since a successful kidney transplantation leads to normalization of the elevated β_2m plasma levels within days. Renal transplantation has been demonstrated to halt progress of the disease, but it is controversial as to whether it can actually lead to regression of established Aβ_2m-amyloid deposits [45, 48–50].

Augmentation of β_2m removal in dialysis patients. Presently available studies can be summarized as follows [2]: Low-flux hemodialyzers with regenerated cellulosic membranes are impermeable for β_2m. High-flux membranes allow substantial removal of β_2m during hemodialysis. Removal can be enhanced further by increasing convective transport, that is, ultrafiltration, such as in hemodiafiltration and hemofiltration. However, a considerable rebound of β_2m plasma levels occurs after treatment, and the absolute amount of β_2m removed decreases with decreasing plasma levels [51, 52]. Therefore, even on a theoretical basis, currently available (nontransplant) treatment options will not allow normalization of β_2m plasma levels [52]. In accordance with this, clinical studies in which β_2m serum levels were determined in patients chronically dialyzed with either regenerated cellulosic or synthetic high-flux membranes usually yielded reductions of the plasma level by about 20 to 30% in the high-flux group only [53–56].

Continuous peritoneal dialysis allows for some β_2m removal and plasma levels in continuous ambulatory peritoneal dialysis (CAPD) patients are about 20 to 30% lower than those of patients on Cuprophane® hemodialysis, provided that they are matched for residual diuresis [57, 58]. However, it is controversial as to whether continuous ambulatory peritoneal dialysis reduces the prevalence of carpal tunnel syndrome in comparison with hemodialysis patients [59, 60].

Adsorbent columns in the hemodialysis circuit have also been used to increase β_2m removal [61–63]. Concerns relating to the relative nonspecificity of β_2m adsorption and consequently the long-term safety of these devices as well as cost issues thus far have prevented broad usage of such columns.

Choice of dialyzer membranes. Various retrospective studies have compared Aβ_2m-amyloid signs in patients treated with either Cuprophane® dialyzers or high-flux hemodialyzers (Table 2). In this setting, the effects of the biocompatibility of the dialyzer membranes cannot be separated from the second approach, that is, increased β_2m removal with the high-flux membrane, nor can it be separated from dialysate variables, which are also influenced by the choice of the dialyzer membrane. The available data on the comparison of Cuprophane and high-flux dialyzers are controversial, with some studies demonstrating a benefit in the high-flux group and others failing to observe a difference in Aβ_2m-amyloid prevalence (Table 2). In part, this discrepancy may be due to the ubiquitous reliance on the presence or absence of carpal tunnel syndrome, which is heavily influenced by the presence of heart disease in uremic patients [44], that is, an uncontrolled variable in the studies cited so far.

Despite these concerns, two large and well-controlled studies suggest that high-flux dialysis or filtration may exert a beneficial effect on the signs of Aβ_2m-amyloidosis: in 1991 van Ypersele de Strihou et al demonstrated that there appears to be a positive effect of long-term treatment with acrylonitrile hemodialyzers on some (bone cystic lesions), although not all (carpal tunnel syndrome) Aβ_2m-amyloidosis–associated symptoms [32]. Locatelli et al noted in 6444 patients of the Lombardy registry that the risk of carpal tunnel syndrome was reduced by 42% in the patients treated with high-flux hemo(dia)filtration even after adjustment for confounding factors such as diabetes or heart disease [44].

Dialysate-related factors. Baz et al noted a dramatic reduction of carpal tunnel syndrome prevalences in patients dialyzed with ultrapure dialysate despite the usage of Cuprophane or cellulose acetate membranes, suggesting that endotoxin or other bacterial products accelerate the clinical manifestation of the amyloidosis [64]. Concerns with this study relate to the fact that hemodialysis was performed only twice weekly and that patient groups were recruited from different dialysis centers [64]. In the Hannover Medical School, we noted an 80% reduction of amyloid signs in our chronic hemodialysis population between 1988 and 1996 [65] but were unable to relate it to the increase in high-flux, synthetic membrane usage. Rather, dialysate factors such as microbiological purity and/or the usage of bicarbonate buffer appeared to be associated with this decrease in prevalence. However, we could not formally exclude that other changes in the general care of ESRD patients between 1988 and 1996 (for example, erythropoietin (EPO) therapy, avoidance of aluminum) could also have contributed to our observation. Finally, Kleophas et al have recently published their long-term experience with a tank dialysis system, which uses essentially pyrogen-free dialysate together with Cuprophane (up to 1992) or high-flux synthetic membranes (from 1992 until evaluation in 1996) [66]. As shown in Figure 1, the prevalence of carpal tunnel

Table 2. Summary of clinical studies investigating the relationship between the type of dialysis treatment and clinical signs of Aβ_2m-amyloidosis

Author	Hemodialysis membrane		Criteria	Outcome[a]
	Cuprophan	High flux		
Chanard 1989 [67]	N = 54	N = 31	CTS	Cu > AN69
Brunner 1990 [68]	N = 55	N = 55	CTS, cysts, pain	Cu = AN69
van Ypersele 1991 [32]	N = 106	N = 115	CTS	Cu = AN69
			cysts	Cu > AN69
Kessler 1991 [69]	N = 95	N = 15	CTS	Cu = AN69
			arthropathy	Cu > AN69
Bonomini 1994 [70]	N = 53	N = 42	CTS	Cu > Synthetic[b]

CTS = carpal tunnel syndrome.
"cysts" = radiolucent bone lesions.
[a] > denotes higher prevalence in patients dialyzed with Cuprophane membranes as compared to those dialyzed with synthetic high flux membranes and = denotes similar prevalence
[b] documented higher prevalence of cardiovascular disease (i.e., a risk factor for CTS) in the "synthetic" group

syndrome in this population compared favorably to that of various other reports.

Based on these considerations, the current pragmatic approach to the prevention of Aβ_2m-amyloidosis includes (*1*) ignoring the issue of Aβ_2m-amyloidosis in all patients whose life expectancy on dialysis is below five years, that is, the time when clinical manifestations first appear (Fig. 1); (*2*) in all others, attempt renal transplantation whenever possible; (*3*) during hemodialysis periods, use bicarbonate-buffered dialysate and attempt to reduce microbiological dialysate contamination as much as possible; and (*4*) use high-flux hemodialysis in those patients at increased risk to develop Aβ_2m-amyloidosis, namely all patients, independent of age, who have little chance of receiving a renal transplant and old patients, independent of whether they are candidates for transplantation.

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